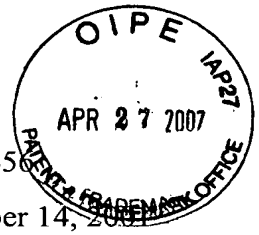
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



In re application of:
ZAUDERER *et al.*
Appl. No. 09/987,456
Filing date: November 14, 2001
For: ***In Vitro* Methods of Producing and Identifying Immunoglobulin Molecules in Eukaryotic Cells**

Confirmation No.: 6770
Art Unit: 1639
Examiner: Epperson, J.D.
Atty. Docket: 1821.0070004/EJH/T-M

Brief on Appeal Under 37 C.F.R. § 41.37

Mail Stop Appeal Brief - Patents

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

A Notice of Appeal from the final rejection of claims 84, 88-97, 99, 103, 107-122, and 127-131 was filed on January 31, 2007. Appellants hereby file this Appeal Brief, together with the required brief filing fee and any necessary extension of time fees.

It is not believed that extensions of time are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

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I. Real Parties in Interest

The real parties in interest in this appeal are the University of Rochester and Vaccinex, Inc. The University of Rochester is the assignee of the present invention by virtue of an assignment from the inventors to Vaccinex, LP (now Vaccinex, Inc.), executed on January 24, 2002, and recorded against the present application on February 7, 2002, beginning at reel 012375/frame 0199; and an assignment from Vaccinex, LP to the University of Rochester, executed on January 24, 2002, and recorded against the present application on February 7, 2002, beginning at reel 012375/frame 0223. Vaccinex, Inc. is the exclusive licensee of the present invention by virtue of an agreement with the University of Rochester.

II. Related Appeals and Interferences

There are no prior or pending appeals, interferences or judicial proceedings known to Appellant or the Appellant's legal representative which may be related to, directly affect or be directly affected by, or have a bearing on the Board's decision in the present Appeal.

III. Status of Claims

Claims 1-83, 123-126, and 127-128* have been canceled.

Claims 84, 88-97, 99, 103, 107-122, and 129-131 are rejected.

Claims 98, 100-102, and 104-106 have been withdrawn from consideration.

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* Claims 127 and 128 are canceled in an Amendment under 37 C.F.R. § 41.33(b), filed concurrently herewith.

IV. Status of Amendments

In an Amendment under 37 C.F.R. § 41.33(b), filed concurrently herewith, Appellants have requested that claims 127 and 128 be canceled.

V. Summary of Claimed Subject Matter

A. Overview of Claimed Subject Matter

Claim 84 is the sole independent claim involved in this appeal. The invention defined by claim 84 relates generally to a method of selecting polynucleotides that encode an antigen-specific human immunoglobulin molecule. The method of claim 1 comprises, *inter alia*, introducing into mammalian host cells: (1) a library of polynucleotides encoding immunoglobulin subunit polypeptides comprising a heavy chain (or light chain) variable and constant region, and (2) a library of polynucleotides encoding immunoglobulin subunit polypeptides comprising a light chain (or heavy chain) variable and constant region, and permitting expression of immunoglobulin molecules from the host cells. The libraries of polynucleotides are constructed in vaccinia virus vectors. If the immunoglobulin molecule is able to specifically bind to an antigen of interest, the vaccinia virus vectors containing the polynucleotides from the first library are recovered. By this method, one can identify from a library of polynucleotide molecules those that encode an immunoglobulin subunit polypeptide comprising a heavy or light chain variable region that is capable of binding to a specific antigen. Support for claim 84 can be found throughout the Specification as filed, for example, at paragraphs [0013]-[0024], [0025]-[0029], [0048]-[0050], [0053]-[0062], [0067]-[0069], [0071]-[0075], [0078]-[0083], [0089]-[0102], [0109]-[0112], [0119]-[0125], [0131]-[0132], [0156], and Examples 1-3, and 18.

B. Advantages of the Present Invention

At the time of the present invention, there were general strategies to produce immunoglobulin molecules that could recognize "self" (*e.g.*, human) antigens and therefore be used for therapeutic and diagnostic purposes. *See* Specification as filed at paragraphs [0003]-[0005]. According to the first strategy, antibodies against such antigens could be raised in rodents. *Id.* However, such rodent antibodies would not be desirable for use in humans, for example, because they could elicit an immune response as a foreign protein. *Id.* Therefore, the antigen binding regions from the rodent antibody could be grafted onto the framework region of a human antibody, a process known as "humanization." *Id.* at paragraph [0005]. However, humanization can diminish binding affinity of the antibody for the target antigen, which can require costly and laborious work to restore. *Id.*

The second strategy uses immunization of transgenic mice that express human immunoglobulin sequences to select an antibody against the antigen of interest. *Id.* at paragraph [0006]. Although the antibodies are derived from sequences that are "human," they may be subject to problem known as "tolerance" which occurs when the human protein against which antibodies are sought has a mouse homologue. When the mouse produces antibodies to the human protein, the antibodies may be biased toward recognizing epitopes that are different between the human and mouse because the mouse will not produce antibodies to epitopes found in its own proteins. *See id.* The drawback is that the "unique" epitopes may not be the optimal targets. *Id*

The third general strategy is an *in vitro* screening approach, whereby bacterial host cells are infected with bacteriophage particles harboring nucleic acids that encode

immunoglobulin fragments fused to a bacteriophage surface protein. *Id.* at paragraph [0007]. When these fusion proteins are expressed, the immunoglobulin fragments are displayed on the surface of the bacteriophage, attached by the surface protein. *Id* This allows for the displayed immunoglobulin fragments to be screened for those fragments that bind an antigen of interest and allows the nucleic acid encoding the immunoglobulin fragment to be recovered. *Id.* However, phage display only results in the expression of a fragment of an antibody, requiring that, the antibody fragment be re-cloned for use as a full antibody. *Id.* at paragraph [0008]. Furthermore, there are different selective filters imposed on the antibodies selected from phage display methods because the antibody fragments may fold differently when expressed as phage fusion proteins than they do when removed from the phage context and expressed as whole antibodies, and because the antibodies do not undergo eukaryotic post-translational modifications. *See id.* at paragraphs [0008]-[0009].

The present invention provides for the direct identification, in mammalian cells, of antigen-specific, fully human antibodies. Such fully human antibodies would be expected to have a lower incidence of immune rejection when used as therapeutics than would fully murine or humanized antibodies. In addition, antibodies identified by the claimed methods do not have to be re-engineered for use as full-length immunoglobulins, unlike antibody fragments isolated from phage display, since the claimed invention provides for direct expression and selection of whole antibodies, with normal post-translational modifications. The present invention further provides the ability to achieve extremely high levels of combinatorial diversity of human immunoglobulin heavy and

light chains *in eukaryotic cells*, which results in an increased likelihood of identifying antibodies with high-affinity, high specificity, and desired functions.

Another advantage of the present invention is the ability to directly select antibodies that would otherwise be difficult or impossible to identify with other antibody selection systems. For example, selecting antibodies via phage display is not generally suitable for use in screening for antibodies that bind to membrane-associated proteins. Such proteins are generally difficult to purify and, therefore, antibodies with specificity for such proteins must usually be screened using whole cells or cell membrane fragments. However, phage particles have non-specific interactions with mammalian cells and thereby interfere with the antibody screening process.

In another example, the present invention overcomes the problem of "tolerance" that occurs when selecting antibodies from transgenic mice because the method is performed *in vitro* and there are no species homologues of the antigen that might result in bias toward antibodies that bind less preferred epitopes. Thus, the present invention provides numerous important and distinct advantages over the previously available antibody selection technologies such as phage display and transgenic mice.

VI. Grounds of Rejection to be Reviewed on Appeal

There are two separate grounds of rejection to be reviewed on Appeal:

(1) ***Rejection Under 35 U.S.C. § 103***: Whether the subject matter of claims 84, 88-97, 99, 103, 107-122, and 127-131 would have been obvious over Rowlands *et al.*, WO 93/01296 ("Rowlands") (Exhibit 1) in view of Zauderer, WO 00/28016 ("Zauderer") (Exhibit 2) and Waterhouse *et al.*, *Nuc. Acids*

Res. 21: 2265-66 (1993) ("Waterhouse") (Exhibit 3). Appellants respectfully traverse this rejection.

(2) ***Rejection for Obviousness-type Double Patenting***: Whether the subject matter of claims 84, 88-97, 99, 103, 107-122, and 127-131 is unpatentable under the judicially-created doctrine of obviousness-type double patenting over claims 1-84 of U.S. Patent Application No. 10/052,942 ("the '942 application"), in view of Rowlands, or over claims 46-128 of U.S. Patent Application No. 10/465,808 ("the '808 application"), in view of Rowlands and Zauderer. Appellants respectfully traverse these rejections.

VII. Argument

A. The Claimed Methods Would Not Have Been Obvious Over the Cited References

1. Legal Principles Relating to Nonobviousness

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki,* 745 F.2d 1468, 1471-73, 223 USPQ 785, 788 (Fed. Cir. 1984). To meet this burden, the Examiner must satisfy three requirements. First, all of the claim limitations must be taught or suggested by the prior art. *See In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974); *see also In re Glaug*, 283 F.3d 1335, 1341-42, 62 USPO2d 1151, 1154 (Fed. Cir. 2002); *In re Rijckaert*, 9 F.3d 1531, 1533, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). Second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in

the art, to modify the reference or to combine references. *See In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). Third, there must be a reasonable expectation of success. *See In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicants' disclosure. *See In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Furthermore, the following tenets of patent law must be followed when applying 35 U.S.C. § 103:

> (1) the claimed invention must be considered as a whole...; (2) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination...; (3) the references must be viewed without the benefit of hindsight vision afforded by the claimed invention...; [and] (4) "ought to be tried" is not the standard with which obviousness is determined ...

Hodosh v. Block Drug Co., Inc. 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 188 n.5 (Fed. Cir. 1986). "[I]t is insufficient to merely identify each element in the prior art to establish unpatentability of the combined subject matter as a whole." *Sanofi-Synthelabo v. Apotex*, 470 F.3d 1368, 1370, 81 USPQ2d 1097, 1104 (Fed. Cir. 2006) (citing *Abbott Labs. v. Andrx Pharm., Inc.*, 452 F.3d 1331, 1336 (Fed Cir. 2006)).

2. Summary of the Examiner's Basis for the Obviousness Rejection

The Examiner alleges that claims 84, 88-97, 99, 103, 107-122, and 127-131 would have been obvious over Rowlands in view of Zauderer and Waterhouse. The Examiner's position is that the skilled artisan would have been motivated to use

Rowlands' method of expressing single, isolated antibody heavy and light chains and to use Zauderer's method of screening a single library of tumor antigens in mammalian cells to make and screen immunoglobulin heavy and light chain libraries as taught in Waterhouse for prokaryotic host cells. *See* Office Action dated October 31, 2006 (referred to herein as "the 10/31/06 Office Action"), at pages 8-10. According to the Examiner, there would have been a reasonable expectation of success because both Rowlands and Zauderer discuss the use of vaccinia virus vectors in mammalian cells, and Waterhouse discloses examples of associated heavy and light chains that can be used for screening and/or antibody maturation in bacteria. *See id.* at pages 3 and 9-10. As explained below, this justification for the rejection is factually flawed and legally insufficient to establish a *prima facie* case of obviousness.

3. Summary of Cited References

(a) Rowlands

Rowlands discloses the introduction of vaccinia virus expression vectors containing the heavy and light chain sequences of a particular, preselected antibody, Campath-1H. Campath-1H is a humanized antibody that binds to CDw52. Campath-1H was generated by grafting the antigen-specific complementarity determining regions (CDRs) of the rat Campath-1G monoclonal antibody onto a human immunoglobulin framework. The Rowlands method is concerned with developing an expression system to increase the yield of a known antibody, preferably a humanized antibody such as Campath-1H. *See* Rowlands at page 3, line 19 to page 4, line 5 and page 8, line 24 to page 9, line 2.

(b) Zauderer

Zauderer discloses a method for identification of target antigens recognized by cytotoxic T cells. The Zauderer method generates a single library of vaccinia virus vectors to express tumor, cancer, or infected cell-specific antigens, which are then screened with cytotoxic T cells to identify reactive target antigens. The reactive antigens can be used as immunogenic compositions or vaccines. *See, e.g.*, Zauderer at cover page (Abstract) and at page 14, line 19 to page 15, line 6.

(c) Waterhouse

Waterhouse discloses a method of using *lox*-Cre regulated site-specific recombination to pair heavy and light chain genes from different replicons into a single bacteriophage-infected bacterial host. Waterhouse at page 2265, column 1. The premise behind the Waterhouse method was to introduce two bacteriophage vectors into *E. coli* bacterial host cells. The first vector was an "fd phage acceptor vector" encoding a light chain fragment of a "first" antibody (specifically, an anti-phOx antibody), and a heavy chain fragment of a "second," different antibody (specifically, an anti-TNF-α antibody). *Id.* The second vector was a "donor vector" encoding the heavy chain fragment of the "first" antibody (*i.e.*, the anti-phOx antibody). Both vectors contained *loxP* sites which, in the presence of Cre recombinase that was also introduced into the bacterial host cells, could recombine to generate chimeric plasmids. *Id.* at column 1-2. As a result of the recombination event, the plasmids could exchange heavy chain fragments to yield plasmids with the light and heavy chain fragments of the first antibody (*i.e.*, a complete anti-phOx Fab fragment), and plasmids with only the heavy chain fragment of the second (*i.e.*, an anti-TNF-α heavy chain). *Id.* at column 2. The acceptor vector also encoded the

phage gene 3 protein (g3p) as a fusion protein with the anti-phOx Fab fragment so that the antibody fragment was displayed on the surface of the phage particles produced by the *E. coli* host cell. *Id.* 2265, column 2 and at page 2266, Figure 1. Waterhouse proposed that the method could be used to make a combinatorial library by providing a light chain fragment repertoire in the first vector and a heavy chain fragment repertoire in the second vector and allowing them to recombine. *Id.* at page 2666, column 1. However, they did not actually perform the method using antibody repertoires in this reference.

4. Claims 84, 88-97, 99, 103, 107-122, and 127-131 Would Not Have Been Obvious over the Cited References

(a) There Was No Reasonable Expectation of Success in Combining the Cited References

One of ordinary skill in the art would not have been motivated to combine Rowlands with Zauderer and Waterhouse with a reasonable expectation of success. The Examiner's position is that,

> one of ordinary skill in the art would have reasonably expected to be successful because Zauderer et al. teach several successful examples of library formation using the same vaccinia virus vectors that are disclosed by Rowlands et al. and Waterhouse et al. teach several successful examples of associated light/heavy chains that can be used for screening and/or antibody maturation, which would encompass the heavy/light chain antibodies disclosed by Rowlands et al.

See 10/31/06 Office Action at page 10. However, the Examiner's conclusion is based on erroneous assumptions made without a supporting scientific rationale and is legally and factually flawed.

As discussed above, Rowlands discloses the expression of vaccinia virus vectors containing the heavy and light chains of the pre-selected humanized Campath-1H antibody. Zauderer discloses a method of screening one vaccinia virus expression library of tumor antigens with cytotoxic T cells. Waterhouse discloses the expression of antibody heavy and light chain fragments in a combinatorial phage display library in bacteria. Even assuming, *arguendo,* that one of ordinary skill in the art would know in view of Rowlands how to express a *single* antibody, and would know in view of Zauderer how to make and screen a *single* vaccinia virus expression library, it does not follow that the skilled artisan could, with a reasonable expectation of success, arrive at a method of selecting polynucleotides encoding antigen-specific immunoglobulins by introducing *two* libraries of vaccinia virus vectors into mammalian host cells. This is so, even in view of Waterhouse, because the Waterhouse method is performed in a completely different biological system than the Rowlands and Zauderer methods.

As evidence that one of skill in the art would not have had a reasonable expectation of success, Appellants point to the Declaration of Dr. Walter J. Storkus ("Storkus Declaration"), filed with the reply on July 21, 2005 (submitted herewith as Exhibit 4). Dr. Storkus is an expert in immunology and was a member of the Scientific Advisory Board (SAB) of Vaccinex, Inc.[†], at the time the present application was filed. *See* Storkus Declaration. As an SAB member, Dr. Storkus evaluated the claimed technology contemporaneously with the filing of the present application and, therefore, was able to provide an account of his thoughts about the invention *at that time.* Dr. Storkus opined that, at the time, he did not think there was a reasonable expectation of

[†] Vaccinex, Inc., is the exclusive licensee of the present invention.

success and he provided specific reasons why he considered phage display methods, such as those in disclosed in Waterhouse, to be of limited instructive value for a eukaryotic immunoglobulin screening method. *Id.* at paragraphs 7-9. Because of the different ways in which prokaryotic and eukaryotic expression systems work and the complexity of getting randomly expressed immunoglobulin heavy and light chains from two different libraries to associate, Dr. Storkus stated that, even in view of the cited references, at the time the present application was filed, he would not have expected to achieve success with the claimed invention. *Id.* Furthermore, Dr. Storkus indicated that a eukaryotic cell system was thought to be impractical for screening a sufficient number of eukaryotic cells to find an antibody that had specificity for a specific antigen of interest. *Id.* at page 3. Hence, the limits on the ability to screen eukaryotic host cells as opposed to phage particles would have been considered an obstacle to the reasonable expectation of success in arriving at the claimed methods by combining Rowlands with Zauderer and Waterhouse.

The Examiner erred by disregarding the Storkus Declaration without providing sound legal or factual bases for doing so. The Examiner erred legally by substituting his opinion for that of an expert without providing any countervailing evidence to support his conclusion. *See In re Zeidler*, 682 F.2d 961, 966-67, 215 USPQ 490, 494 (C.C.P.A. 1982) (holding that the decision of the Board of Patent Appeals and Interferences constituted reversible error, "the board having erroneously substituted its judgment for that of an established expert in the art."). For example, the Examiner relies on Waterhouse to show "that the production of two libraries ... will lead to more favorable antibodies via a co-selection process, regardless of how those antibodies are produced,"

10/31/06 Office Action at page 30 (emphasis in original), and has asserted that "the prokaryotic/eukaryotic distinctions to which Applicants refer ... are not at issue in this case." Office Action of April 21, 2006, at page 28. However, as shown by the Storkus Declaration, these differences are at the *very heart* of why one of skill in the art would not have had a reasonable expectation of success in combining Waterhouse with Rowlands and Zauderer. *See* Storkus Declaration at paragraphs 7-9.

In particular, Dr. Storkus stated: 1) that he thought that it would not be practical to screen the number of eukaryotic cells necessary to find antigen-specific antibodies, as was possible via screening phage; and 2) because of the differences in the conditions of eukaryotic cytoplasm as compared to prokaryotic periplasm, he thought that random pairs of immunoglobulin heavy and light chains would fail to associate properly in eukaryotic cells and therefore would not allow selection of antigen-specific antibodies. *Id.* at paragraph 7. Dr. Storkus further explained that expressing a single antibody, as in Rowlands, is "far simpler" than expressing heavy and light chain pairs from separate libraries, because the Rowlands antibody had already been selected for heavy and light chains that paired correctly and efficiently to specifically bind antigen. *Id.* at paragraph 9. Dr. Storkus also explicitly stated that Zauderer does not address the concern of assembling heavy and light chains from two *separate* libraries in eukaryotic cells because only one library was introduced into host cells. *Id.* Therefore, Dr. Storkus concluded that his expectations would not have changed in view of these references. *Id.*

The Examiner has provided no specific evidence or relevant scientific rationale to counter the statements of Dr. Storkus or support the erroneous assumption that, simply because two libraries had been used for phage display in prokaryotic cells, one of skill in

the art would expect the claimed two-library screening/expression system to be successful in eukaryotic cells. Indeed, the only "evidence" cited by the Examiner are passages from Rowlands, Zauderer, and Waterhouse, and a few paragraphs from Appellants' own specification that mention phage display methods (and, more specifically, the shortcomings of phage display methods). *See* 10/31/06 Office Action at pages 22-23 and 29. Dr. Storkus gave explicit reasons why he did not think there was a reasonable expectation of success, even in view of Rowlands, Zauderer, and Waterhouse. Hence, citing excerpts from these references does not lend support to the Examiner's position. Likewise, the cited paragraphs from Appellants' own specification do not support the Examiner's position because Appellants do not dispute the fact that combinatorial libraries for selecting immunoglobulins have been generated using bacteriophage. Rather, the relevant inquiry is whether one of skill in the art would have had been motivated to combine Rowlands, Zauderer, and a phage display reference like Waterhouse to arrive at the claimed invention *with a reasonable expectation of success*. Dr. Storkus explained why he, in his opinion as an immunology expert who evaluated the claimed technology at the time the present application was filed, did not think there was a reasonable expectation of success at that time. By disregarding Dr. Storkus's explanation without providing any supporting evidence to contrary, the Examiner has improperly substituted his own opinion for that of an expert.

In addition, the Examiner erred factually by contending that the Storkus Declaration is "ambiguous," and that Dr. Storkus did not specify the time at which the idea for the present invention was first presented to him. *See* 10/31/06 Office Action at page 30. It is clear from his Declaration that the idea was presented to Dr. Storkus in his

capacity as an SAB member of Vaccinex, Inc., and that he was an SAB member at the time the present application was filed (*i.e.*, from 2001 to 2004). *See* Storkus Declaration at pages 1-2.

One of ordinary skill in the art would not have expected that, simply because Waterhouse *et al.* had developed a method of screening antibody fragments fused to phage particles in *bacterial host cells*, the same thing could be done with two separate libraries of vaccinia viruses in *eukaryotic host cells*. There simply is not sufficient guidance in any of the cited references to indicate how one of ordinary skill in the art would have combined them with a reasonable expectation of success. Furthermore, the Examiner has not pointed to any evidence other than Appellants' own specification to suggest that there was a reasonable expectation of success; but this is an improper source for this expectation. *See, e.g., In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438. As such, the Examiner has not established a *prima facie* case of obviousness.

(b) The Examiner has not Considered the Claimed Invention as a Whole and is Using Impermissible Hindsight

It is well established that "[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988) Furthermore, "rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be 'an illogical and inappropriate process by which to determine patentability.'" *In re Rouffet*, 149 F.3d 1350, 1375 47 U.S.P.Q.2d 1453 (Fed. Cir. 1998)

(quoting *Sensonics, Inc. v. Aerosonic Corp.* 81 F.3d 1566, 1570, 38 U.S.P.Q.2d 1551, 1554 (Fed. Cir. 1996).

It is also well established that the invention must be considered "as a whole," and that the Examiner cannot merely focus on the obviousness of differences and substitutions between the claimed invention and the cited references to establish a *prima facie* case of obviousness. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 USPQ 81, 92 (Fed. Cir. 1986) ("Focusing on the obviousness of substitutions and differences instead of on the invention as a whole as the district court did in frequently describing the claimed invention as *the mere substitution of monoclonal for polyclonal antibodies in a sandwich assay*, was a legally improper way to simplify the difficult determination of obviousness." (emphasis added)).

In the instant case, the Examiner has distilled the claimed invention to its gist of "a method of selecting an antibody from two expression libraries" Using this "gist" of the invention, the Examiner has selectively picked individual elements of the claimed invention from the cited references to assert a *prima facie* case of obviousness. In doing so, however, the Examiner has used impermissible hindsight and failed to consider the claimed invention as a whole. The claimed invention requires the introduction into mammalian cells of two libraries of vaccinia virus vectors, one encoding immunoglobulin heavy chains and one encoding immunoglobulin light chains, wherein the expressed immunoglobulin chains can combine to form immunoglobulin molecules, thus permitting expression of immunoglobulin molecules from mammalian host cells. The cited references do not teach or suggest the claimed invention *as a whole*.

Rowlands discloses expression of a pre-selected Campath-1H antibody by introducing into a mammalian host cell a single, pre-selected Campath 1-H heavy chain and a single, pre-selected Campath-1H light chain in vaccinia virus vectors. However, Rowlands does not teach expression of a *library* of heavy chains and a *library* of light chains, so the Examiner relies on Zauderer for the feature of expressing a library of vaccinia virus vectors. *See* Office Action at pages 5-6. But this combination still does not teach all elements of the claimed invention because it does not teach that *two* vaccinia virus libraries of *immunoglobulin heavy and light chains* are introduced and expressed in mammalian host cells. *See id.* Therefore, the Examiner relies on Waterhouse as a tertiary reference, stating that it discloses screening of two libraries of immunoglobulin heavy and light chains. *See id.* at page 6. However, of significant importance, the Waterhouse method uses bacteriophage vectors introduced into *prokaryotic* bacterial host cells, which is a key difference from the claimed invention.

The Examiner has focused on this difference between the claimed invention and the combination of the Rowlands and Zauderer references and merely substituted the feature of two expression libraries from Waterhouse to "fill in" the missing element from the Rowlands/Zauderer combination. However, as established in *Hybritech*, this type of simple substitution of elements is an improper analysis for establishing a *prima facie* case of obviousness. Furthermore, this substitution relies on an improper distillation of the invention down to its gist of "a method of selecting an antibody from two expression libraries," since it ignores the fact that the Waterhouse immunoglobulin libraries are *prokaryotic* phage display libraries and the claimed invention requires two *eukaryotic* expression libraries.

As indicated in the declarations of Dr. Storkus (Exhibit 4) and Dr. Maurice Zauderer (submitted herewith as Exhibit 5), the expression of antibody fragments in prokaryotic phage display libraries is fundamentally different from the expression of immunoglobulins from two eukaryotic libraries and, therefore, the success of the prokaryotic system would not have been predictive of the success of the eukaryotic system. For example, at the time the present application was filed, Dr. Storkus thought that antigen-specific antibodies of interest would not occur at a sufficiently high frequency when expressed from two random libraries of heavy and light chains to permit their identification within the screening throughput parameters of eukaryotic cells. Storkus Declaration at page 3. Also, both Dr. Storkus and Dr. Zauderer indicated that prokaryotic cells and eukaryotic cells would provide different environments for the pairing of immunoglobulin heavy and light chains. Specifically, Dr. Storkus stated that "antibody fragments expressed in phage, whether or not covalently linked, concentrate and are assembled in the periplasmic space." Storkus Declaration at pages 3-4, paragraph 7. Likewise, Dr. Zauderer indicated that one of ordinary skill in the art would not have considered the Waterhouse improvements to phage display methods, *e.g.*, *lox*-Cre recombination of heavy and light chains to allow for simultaneous co-selection from the same prokaryotic host, "as features that could be expanded for use in eukaryotic systems." Zauderer Declaration at pages 6-7. Thus, although immunoglobulin fragments could pair together when concentrated in the periplasmic space of a bacterium, the skilled artisan would not have thought to combine Rowlands and Zauderer with Waterhouse because it would not have been predictable that separately expressed heavy and light chains from two random vaccinia libraries would find each other in the eukaryotic cytoplasm and pair together with sufficient frequency to form antigen-specific

immunoglobulins. It is only by using the claimed invention itself as a roadmap that the Examiner has found the claimed invention to be obvious over this combination of references.

At the very most, the combination of Rowlands, Zauderer, and Waterhouse might be an *invitation to try* introducing two expression libraries of immunoglobulin chains in eukaryotic host cells, "but [the cited references] do not suggest how that end might be accomplished." *See e.g., Hybritech* 802 F.2d at 1380, 231 USPQ at 91. Furthermore, it is well known that "obvious to try" is not the standard for establishing a *prima facie* case of obviousness under 35 U.S.C. § 103. *See e.g., id.*

Accordingly, the Examiner has failed to make a *prima facie* showing of obviousness.

5. Claims 84, 88-97, 99, 103, 107-122, and 129-131 are not Unpatentable for Non-statutory Double Patenting

Claims 84, 88-97, 99, 103, 107-122, and 129-131 are not unpatentable under the doctrine of non-statutory obviousness-type double patenting over claims 1-84 of U.S. Patent Application Serial No. 10/052,942 ("the '942 application"), in view of Rowlands, or over claims 46-128 of U.S. Patent Application Serial No. 10/465,808 ("the '808 application"), in view of Rowlands and Zauderer.

Appellants respectfully request that these rejections be held in abeyance until the remaining issues outstanding in this application have been resolved.

In addition, Appellants note that the '942 application was filed on January 23, 2002, and the '808 application was filed on June 20, 2003, while the present application was filed on November 14, 2001. According to the MPEP § 804.I.B.1 (pg. 800-17):

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.

Thus, if the nonstatutory obviousness-type double patenting rejection over the '942 application, in view of Rowlands is the only rejection remaining in the above-captioned application (*i.e.*, the "earlier filed of the two pending applications"), the double patenting rejection should be withdrawn without the need for a terminal disclaimer. Likewise, if the nonstatutory obviousness-type double patenting rejection over the '808 application, in view of Rowlands and Zauderer is the only rejection remaining in the above-captioned application (*i.e.*, the "earlier filed of the two pending applications"), this double patenting rejection should also be withdrawn without the need for a terminal disclaimer.

B. Conclusions

In view of the foregoing discussion, Appellants submit that the subject matter of claims 84, 88-97, 99, 103, 107-122, and 129-131 would not have been obvious over the cited references. The Examiner has failed to establish that, when considering the claimed invention as a whole and without the use of impermissible hindsight, all of the elements of the claims are taught or suggested by the cited references. The Examiner has

also failed to provide legally and factually sufficient evidence as to why a person of ordinary skill in the art would have been motivated to modify or combine the references with a reasonable expectation of success. Thus, a *prima facie* case of obviousness under 35 U.S.C. § 103 has not been established.

Appellants also submit that, if the nonstatutory obviousness-type double patenting rejection of claims 84, 88-97, 99, 103, 107-122, and 129-131 over the '942 application, in view of Rowlands or over the '808 application in view of Rowlands and Zauderer are the only rejections remaining in the above-captioned application, the double patenting rejections should be withdrawn without the need for terminal disclaimers.

Accordingly, Appellants respectfully request that the Board reverse the Examiner's obviousness and obviousness-type double patenting rejections and remand this application for issue.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Tracy L. Muller
Attorney for Appellants
Registration No. 55,472

Date: April 27, 2007

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

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VIII. Claims Appendix

84. A method of selecting polynucleotides which encode an antigen-specific human immunoglobulin molecule, comprising:

(a) introducing into a population of mammalian host cells capable of expressing said immunoglobulin molecule and permissive for vaccinia virus infectivity, a first library of polynucleotides encoding, through operable association with a transcriptional control region, a plurality of first immunoglobulin subunit polypeptides, each first immunoglobulin subunit polypeptide comprising:

(i) a first immunoglobulin constant region selected from the group consisting of a heavy chain constant region and a light chain constant region,

(ii) an immunoglobulin variable region selected from the group consisting of a heavy chain variable region and a light chain variable region, wherein said variable region corresponds to said first constant region, and

(iii) a signal peptide capable of directing cell surface expression or secretion of said first immunoglobulin subunit polypeptide,

wherein said first library is constructed in a vaccinia virus vector, provided said first library is not constructed by traditional homologous recombination;

(b) introducing into said host cells a second library of polynucleotides encoding, through operable association with a transcriptional control region, a plurality of second immunoglobulin subunit polypeptides, each comprising:

(i) a second immunoglobulin constant region selected from the group consisting of a heavy chain constant region and a light chain constant region,

wherein said second immunoglobulin constant region is not the same as said first immunoglobulin constant region,

(ii) an immunoglobulin variable region selected from the group consisting of a heavy chain variable region and a light chain variable region, wherein said variable region corresponds to said second constant region, and

(iii) a signal peptide capable of directing cell surface expression or secretion of said second immunoglobulin subunit polypeptide,

wherein said second immunoglobulin subunit polypeptide is capable of combining with said first immunoglobulin subunit polypeptide to form an immunoglobulin molecule, and wherein said second library is constructed in a vaccinia virus vector, provided said second library is not constructed by traditional homologous recombination;

(c) permitting expression of immunoglobulin molecules, from said host cells;

(d) contacting said immunoglobulin molecules with an antigen and detecting specific antigen-antibody complexes; and

(e) recovering vaccinia virus vectors containing polynucleotides of said first library which encode immunoglobulin subunit polypeptides which, as part of an immunoglobulin molecule, are specific for said antigen.

85. The method of claim 84, wherein the vaccinia virus vectors containing said second library of polynucleotides are rendered incapable of producing infectious vaccinia virus virions in said host cells.

86. The method of claim 85, further comprising:

(f) introducing the vaccinia virus vectors recovered in (e) into a population of mammalian host cells capable of expressing said immunoglobulin molecule and permissive for vaccinia virus infectivity;

(g) introducing into said host cells said second library of polynucleotides;

(h) permitting expression of immunoglobulin molecules, from said host cells;

(i) contacting said immunoglobulin molecules with said antigen and detecting specific antigen-antibody complexes; and

(j) recovering vaccinia virus vectors containing polynucleotides of said first library which encode immunoglobulin subunit polypeptides which, as part of an immunoglobulin molecule, are specific for said antigen.

87. The method of claim 86, further comprising repeating steps (f)-(j) one or more times, thereby enriching for polynucleotides of said first library which encode a first immunoglobulin subunit polypeptide which, as part of an immunoglobulin molecule, specifically binds said antigen.

88. The method of claim 84, further comprising isolating the immunoglobulin subunit polypeptide-encoding polynucleotides contained in the vaccinia virus vectors recovered from said first library.

89. The method of claim 88, further comprising:

(k) introducing into a population of mammalian host cells capable of expressing said immunoglobulin molecule and permissive for vaccinia virus infectivity vaccinia virus vectors containing said second library of polynucleotides, wherein said vaccinia virus vectors are infectious;

(l) introducing into said host cells vaccinia virus vectors containing those polynucleotides isolated from said first library, wherein the vaccinia virus vectors containing said isolated polynucleotides are rendered incapable of producing infectious vaccinia virus vectors in said host cells;

(m) permitting expression of immunoglobulin molecules from said host cells;

(n) contacting said immunoglobulin with said specific antigen and detecting specific antigen-antibody complexes; and

(o) recovering vaccinia virus vectors containing polynucleotides of said second library which encode immunoglobulin subunit polypeptides which, as part of an immunoglobulin molecule, are specific for said antigen.

90. The method of claim 89, further comprising:

(p) introducing the vaccinia virus vectors recovered in (o) into a population of mammalian host cells capable of expressing said immunoglobulin molecule and permissive for vaccinia virus infectivity;

(q) introducing into said host cells vaccinia virus vectors containing those polynucleotides isolated from said first library, wherein the vaccinia virus vectors

containing said isolated polynucleotides are rendered incapable of producing infectious vaccinia virus virions in said host cells;

(r) permitting expression of immunoglobulin molecules from said host cells;

(s) contacting said immunoglobulin molecules with said antigen and detecting specific antigen-antibody complexes; and

(t) recovering vaccinia virus vectors containing polynucleotides of said second library which encode immunoglobulin subunit polypeptides which, as part of an immunoglobulin molecule, are specific for said antigen.

91. The method of claim 90, further comprising repeating steps (p)-(t) one or more times, thereby enriching for polynucleotides of said second library which encode a second immunoglobulin subunit polypeptide which, as part of an immunoglobulin molecule, specifically binds said antigen.

92. The method of claim 91, further comprising isolating the immunoglobulin subunit polypeptide-encoding polynucleotides contained in the vaccinia virus vectors recovered from said second library.

93. A method of producing a first polynucleotide and a second polynucleotide which encode an antigen-specific human immunoglobulin molecule comprising combining a first polynucleotide and a second polynucleotide isolated according to claim 92.

94. A method of producing a host cell which expresses an antigen-specific human immunoglobulin molecule comprising introducing the first and second polynucleotides produced as recited in claim 93 into a mammalian host cell capable of expressing said first and second polynucleotides.

95. A method of producing an antigen-specific human immunoglobulin molecule comprising:

culturing a host cell produced according to the method of claim 94 under conditions wherein said first and second polynucleotides are expressed; and

recovering said antigen-specific human immunoglobulin molecule.

96. The method of claim 84, wherein said plurality of first immunoglobulin subunit polypeptides are immunoglobulin heavy chains.

97. The method of claim 84, wherein said plurality of first immunoglobulin subunit polypeptides are immunoglobulin light chains.

98. The method of claim 85, wherein said host cells are infected with said first library at an MOI ranging from about 1 to about 10, and wherein said second library is introduced under conditions which allow up to 20 vaccinia virus vectors of said second library to be taken up by each infected host cell.

99. The method of claim 89, wherein said host cells are infected with said second library at an MOI ranging from about 1 to about 10.

100. The method of claim 84, wherein said transcriptional control region comprises a poxvirus promoter.

101. The method of claim 100, wherein said promoter is a vaccinia virus p7.5 promoter.

102. The method of claim 100, wherein said promoter is a vaccinia MH-5 promoter.

103. The method of claim 84, wherein said transcriptional control region comprises a T7 phage promoter active in cells in which T7 RNA polymerase is expressed.

104. The method of claim 84, wherein said transcriptional control region comprises a transcriptional termination region.

105. The method of claim 84, wherein said vaccinia virus vector is attenuated.

106. The method of claim 105, wherein said vaccinia virus vector is deficient in D4R synthesis.

107. The method of claim 84, wherein said first library of polynucleotides is constructed by a method comprising:

(a) cleaving an isolated vaccinia virus genome to produce a first viral fragment and a second viral fragment, wherein said first fragment is nonhomologous with said second fragment;

(b) providing a population of transfer plasmids comprising said polynucleotides which encode said plurality of immunoglobulin heavy or light chains, or fragments thereof through operable association with a transcription control region, flanked by a 5' flanking region and a 3' flanking region, wherein said 5' flanking region is homologous to a terminal portion of said first viral fragment and said 3' flanking region is homologous to a terminal portion of said second viral fragment; and wherein said transfer plasmids are capable of homologous recombination with said first and second viral fragments such that a viable vaccinia virus genome is formed;

(c) introducing said transfer plasmids and said first and second viral fragments into a mammalian host cell permissive for vaccinia virus infectivity under conditions wherein said transfer plasmids and said viral fragments undergo in vivo homologous recombination, thereby producing a viable modified vaccinia virus genome comprising a polynucleotide which encodes an immunoglobulin heavy chain or an immunoglobulin light chain; and

(d) recovering said modified vaccinia virus genome.

108. The method of claim 107, wherein said vaccinia virus genome is selected from the group consisting of a v7.5/tk virus genome and a vEL/tk virus genome.

109. The method of claim 107, wherein said first viral fragment and said second viral fragment are generated by cleaving one or more unique restriction sites selected from the group consisting of a unique NotI restriction site, a unique ApaI restriction site, and a combination of a unique NotI restriction site and a unique ApaI restriction site, in the tk gene of said vaccinia virus genome.

110. The method of claim 84, wherein said second library of polynucleotides is constructed by a method comprising:

(a) cleaving an isolated vaccinia virus genome to produce a first viral fragment and a second viral fragment, wherein said first fragment is nonhomologous with said second fragment;

(b) providing a population of transfer plasmids comprising said polynucleotides which encode said plurality of immunoglobulin light or heavy chains, or fragments thereof through operable association with a transcription control region, flanked by a 5' flanking region and a 3' flanking region, wherein said 5' flanking region is homologous to a terminal portion of said first viral fragment and said 3' flanking region is homologous to a terminal portion of said second viral fragment; and wherein said transfer plasmids are capable of homologous recombination with said first and second viral fragments such that a viable vaccinia virus genome is formed;

(c) introducing said transfer plasmids and said first and second viral fragments into a mammalian host cell permissive for vaccinia virus infectivity under conditions wherein said transfer plasmids and said viral fragments undergo homologous recombination, thereby producing a viable modified vaccinia virus genome comprising a

polynucleotide which encodes an immunoglobulin light chain or an immunoglobulin heavy chain; and

(d) recovering said modified vaccinia virus genome.

111. The method of claim 110, wherein said vaccinia virus genome is selected from the group consisting of a v7.5/tk virus genome and a vEL/tk virus genome.

112. The method of claim 110, wherein said first viral fragment and said second viral fragment are generated by cleaving one or more unique restriction sites selected from the group consisting of a unique NotI restriction site, a unique ApaI restriction site, and a combination of a unique NotI restriction site and a unique ApaI restriction site, in the tk gene of said vaccinia virus genome.

113. The method of claim 96, wherein said immunoglobulin heavy chains are a secreted form of an immunoglobulin heavy chain.

114. The method of claim 113,

wherein vaccinia virus vectors containing said first library of polynucleotides are divided into a plurality of virus pools, and each virus pool is infected into a separate population of mammalian host cells to form a plurality of host cell pools;

wherein said host cell pools are cultured such that immunoglobulin molecules are expressed and secreted into the culture medium containing said host cell pools to form a plurality of immunoglobulin pools;

wherein said immunoglobulin pools are contacted with said antigen, and specific antigen-antibody complexes are detected; and

wherein vaccinia virus vectors are recovered from those host cell pools which expressed immunoglobulin pools from which specific antigen-antibody complexes were detected.

115. The method of claim 114, further comprising:

(a) dividing said recovered vaccinia virus vectors into a plurality of virus sub-pools and infecting each virus sub-pool into a separate population of mammalian host cells to form a plurality of host cell sub-pools;

(b) culturing said host cell sub-pools such that immunoglobulin molecules are expressed and secreted into the culture medium containing said host cell sub-pools to form a plurality of immunoglobulin sub-pools;

(c) contacting said immunoglobulin sub-pools with said antigen, and detecting specific antigen-antibody complexes; and

(d) recovering vaccinia virus vectors from those host cell sub-pools which expressed immunoglobulin sub-pools from which specific antigen antibody complexes were detected.

116. The method of claim 115, further comprising repeating steps (a)-(d) one or more times, thereby enriching for polynucleotides of said first library which encode a first immunoglobulin subunit polypeptide which, as part of an immunoglobulin molecule specifically binds said antigen.

117. The method of claim 97, wherein said second immunoglobulin subunit polypeptides are a secreted form of an immunoglobulin heavy chain.

118. The method of claim 117,

wherein vaccinia virus vectors containing said first library of polynucleotides are divided into a plurality of virus pools, and each virus pool is infected into a separate population of mammalian host cells to form a plurality of host cell pools;

wherein said host cell pools are cultured such that immunoglobulin molecules are expressed and secreted into the culture medium containing said host cell pools to form a plurality of immunoglobulin pools;

wherein said immunoglobulin pools are contacted with said antigen, and specific antigen-antibody complexes are detected; and

wherein vaccinia virus vectors are recovered from those host cell pools which expressed immunoglobulin pools from which specific antigen antibody complexes were detected.

119. The method of claim 118, further comprising:

(a) dividing said recovered vaccinia virus vectors into a plurality of virus sub-pools and infecting each virus sub-pool into a separate population of mammalian host cells to form a plurality of host cell sub-pools;

(b) culturing said host cell sub-pools such that immunoglobulin molecules are expressed and secreted into the culture medium containing said host cell sub-pools to form a plurality of immunoglobulin sub-pools;

(c) contacting said immunoglobulin sub-pools with said antigen, and detecting specific antigen-antibody complexes; and

(d) recovering vaccinia virus vectors from those host cell sub-pools which expressed immunoglobulin sub-pools from which specific antigen antibody complexes were detected.

120. The method of claim 119, further comprising repeating steps (a)-(d) one or more times, thereby enriching for polynucleotides of said first library which encode a first immunoglobulin subunit polypeptide which, as part of an immunoglobulin molecule specifically binds said antigen.

121. The method of claim 114, wherein said detecting is by ELISA.

122. The method of claim 118, wherein said detecting is by ELISA.

129. The method of claim 84, wherein step (e) further comprises recovering vaccinia virus vectors containing polynucleotides of said second library which encode immunoglobulin subunit polypeptides which, as part of an immunoglobulin molecule are specific for said antigen.

130. The method of claim 129, further comprising isolating the immunoglobulin subunit polypeptide-encoding polynucleotides contained in the vaccinia virus vectors recovered from said second library.

131. A method of producing a first polynucleotide and a second polynucleotide which encode an antigen-specific human immunoglobulin molecule comprising combining a first polynucleotide and a second polynucleotide isolated according to claim 130.

IX. Evidence Appendix

Exhibit	Title of Exhibit	Location in Record
Exhibit 1	Rowlands *et al.*, PCT Publication No. WO 93/01296	Submitted in an Information Disclosure Statement filed by Applicants on November 6, 2002, and first cited by Examiner in Office Action dated September 7, 2004.
Exhibit 2	Zauderer, PCT Publication No. WO 00/28016	Submitted in an Information Disclosure Statement filed by Applicants on May 28, 2002, and first cited by Examiner in Office Action dated September 7, 2004.
Exhibit 3	Waterhouse *et al.*, *Nuc. Acids Res.* 21: 2265-66 (1993)	Submitted in an Information Disclosure Statement filed by Applicants on May 1, 2003, and first cited by Examiner in Office Action dated September 7, 2004.
Exhibit 4	Declaration under 37 C.F.R. § 1.132 of Dr. Walter J. Storkus, including accompanying documents: ▪ *Curriculum vitae* of Dr. Storkus ▪ "Monoclonal Antibody Partnerships in the Biopharmaceutical Industry," excerpts from L.E.K. consulting report (2001). ▪ H. J. de Haard *et al., J. Biol. Chem.* 274:18218-18230 (1999).	Submitted by Applicants with the Reply filed on July 21, 2005.
Exhibit 5	Declaration under 37 C.F.R. § 1.132 of Dr. Maurice Zauderer, including accompanying documents: ▪ *Curriculum vitae* of Dr. Zauderer ▪ Press releases of business alliances with Vaccinex, Inc.	Submitted by Applicants with the Reply filed on July 21, 2005.

X. Related Proceedings Appendix

No decisions have been rendered by a court or the Board in any related proceeding.